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Hybrid Simulation of Heterogeneous Cell Populations

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ABSTRACT The modeling of heterogeneous dynamic cell populations based on population balance equations is an important tool to describe the interaction between intracellular dynamics and population dynamics. However, the numerical simulation of such models remains challenging for models with high-dimensional intracellular dynamics, when these dynamics influence the growth rate of the cells. To cope with this challenge, we propose a hybrid simulation scheme based on the method of partial characteristics. We show that important features of the population density function, such as its moments or marginals, can be approximated by this scheme in a statistically converging way. In a case study with a population of differentiating cells, we illustrate how to obtain the growth dynamics of the individual subpopulations and deduce the extent of cell differentiation under a time-varying stimulus.

INDEX TERMS Cell population dynamics, Monte Carlo (MC) methods, population balance equations (PBEs).

I. INTRODUCTION

In the past decades, population balance equations (PBEs) have emerged as a useful computational tool to model and simulate dynamic heterogeneous cell populations [6], [8]. In these models, a number density function describes the distribution of continuous state variables within the population. Dynamics on the state variables together with source and sink terms due to cell division and death yield a partial differential equation, where the cellular state variables are the independent variables in addition to time. While PBEs make it easy to model cell proliferation and death rates depending on the cellular state, it is challenging to simulate models with high-dimensional intracellular dynamics, due to the resulting large number of independent variables. Classical solution approaches relying on mesh-based methods [2] cannot deal well with this challenge, even though specifically tailored hierarchical approaches may reduce the associated computational burden [7]. As an alternative to mesh-based methods, some classes of PBEs can be solved with the method of characteristics, which is particularly interesting for high-dimensional models. Recently, an exact hybrid simulation scheme for PBEs that uses the method of characteristics has been proposed [10]. However, this is applicable only to a quite restricted class of models, essentially without interactions between the intracellular dynamics and the cell growth.

With this letter, we introduce a new hybrid approach to simulate PBEs as a model for heterogeneous cell populations, which particularly aims at models with high-dimensional intracellular dynamics. Our approach is based on Monte Carlo (MC) simulation for one part of the population dynamics via the method of characteristics in the first step, while the other part is solved as a low-dimensional PBE with a mesh-based method.

II. METHODS

A. MONTE CARLO INTEGRATION

We consider a population balance model given by

$$\frac{\partial N}{\partial t}(t,x) + \operatorname{div}(f(x)N(t,x)) = -b(x)N(t,x) - d(x)N(t,x) + \int_{\Omega} 2b(\xi)\varphi(x,\xi)N(t,\xi)d\xi \tag{1}$$

where $x \in \Omega$ is the vector of intracellular variables, $N(t,x)$ is the cell number density function, $f(x)$ is the intracellular dynamics, $b(x)$ is the cell division rate, $d(x)$ is the dilution rate, and $\varphi(x,\xi)$ is the cell division kernel, defining the probability density that a newborn cell with intracellular variable x had a mother with intracellular variable ξ.

In a sample-based approach, integration over the number density function for computing marginals or moments can be approximated by MC integration. Thereby, the integral of a function $g(x)$ is computed via a sum of function values $g(x_i)$ evaluated at K randomly chosen samples x_i. When using importance sampling, the samples x_i are distributed according

to a probability density function $p(x)$. The MC approximation of the integral is then

$$\int_\Omega g(x)dx \approx \frac{1}{K}\sum_{i=1}^{K}\frac{g(x_i)}{p(x_i)}. \tag{2}$$

With the method of characteristics, the distribution of the samples $p(x_i)$ is time varying. We denote by $p_t(x_i)$ the probability density function for the distribution of samples at time t. It evolves according to

$$\frac{\partial p_t}{\partial t}(x) + \operatorname{div}(f(x)p_t(x)) = 0 \tag{3}$$

which is just the original PBE (1) with a zero right-hand side. For each characteristic trajectory $x(t)$, this can directly be solved with the method of characteristics, yielding the differential equation

$$\dot{p}_t(x_i(t)) = -\operatorname{div}\big(f(x_i(t))\big)p_t(x_i(t)). \tag{4}$$

Based on (4), we introduce a weight factor for each characteristic trajectory $w_i(t) = \big(p_t(x_i(t))\big)^{-1}$ with the dynamics

$$\dot{w}_i(t) = \operatorname{div}(f(x_i(t)))w_i(t). \tag{5}$$

B. METHOD OF CHARACTERISTICS

The proposed simulation method relies on a separation of the intracellular state space $\Omega = \Omega_y \times \Omega_z$. Hereby, Ω_y corresponds to cell growth variables (e.g., cell volume and cell cycle variable), and Ω_z corresponds to intracellular nongrowth variables (e.g., concentrations of signaling molecules). The state vector is split accordingly as $x = (y, z)$. We make the following key assumptions relating to that separation.

1) Cell division rate b depends only on y. For ease of notation, we just write $b(y)$ instead of $b(x)$.
2) Nongrowth variables z do not change upon cell division, i.e., the division kernel can be decomposed as

$$\varphi(x, x') = \varphi(y, y')\prod_{i=1}^{n_z}\delta(z_i - z_i') \tag{6}$$

where δ is the Dirac measure.
3) The intracellular dynamics can be decomposed as

$$f(x) = \begin{pmatrix} f_y(y, z) \\ f_z(z) \end{pmatrix}. \tag{7}$$

Let $z(\cdot) : \mathbb{R} \to \Omega_z$ be a function that satisfies the characteristic equation for the nongrowth variables

$$\dot{z}(t) = f_z(z(t)). \tag{8}$$

The solution of the ODE (8) for an initial condition z_0 is a characteristic trajectory with that initial condition. To each characteristic trajectory, we also assign a weight $w > 0$, which is characterized by the ODE

$$\dot{w} = \operatorname{div}_z\big(f_z(z(t))\big)w. \tag{9}$$

Define

$$\tilde{N}(t, y) = N(t, y, z(t))w(z(t)) \tag{10}$$

and note that

$$\frac{\partial \tilde{N}}{\partial t}(t, y) = \frac{\partial N}{\partial t}(t, y, z(t))w(t) + \frac{\partial N}{\partial z}(t, y, z(t))f_z(z(t))w(t) + N(t, y, z(t))\operatorname{div}_z\big(f_z(z(t))\big)w(t).$$

For a fixed characteristic trajectory $z(t)$, we then obtain the following equation for the density function $\tilde{N}(t, y)$ from the general PBE (1):

$$\frac{\partial \tilde{N}}{\partial t}(t, y) + \operatorname{div}_y(f_y(y, z(t))\tilde{N}(t, y)) = -b(y)\tilde{N}(t, y) - d(y, z(t))\tilde{N}(t, y) + \int_{\Omega_y} 2b(\eta)\varphi(y, \eta)\tilde{N}(t, \eta)d\eta. \tag{11}$$

The growth-related PBE (11) is discretized using the cell average technique (CAT) [5] and solved numerically on a geometric grid along each characteristic trajectory $z^{(i)}(t)$. The CAT is robust, simple in implementation, and computationally efficient in comparison with other sectional methods and preserves several moments quite accurately [3].

III. RESULTS

A. HYBRID SIMULATION SCHEME

In this section, we present a novel hybrid simulation scheme for separable PBEs as discussed in Section II-B. The scheme consists of an MC-based part and a deterministic simulation part. The first part generates a family of characteristic trajectories $z(t)$ with associated weights $w(t)$ by MC simulation. The second part then solves the growth-related PBE (11) along each characteristic trajectory with the CAT.

1) Generate samples $z_0^{(i)}$, $i = 1, \ldots, K$, in the nongrowth variables z. If possible, the samples are drawn from the initial marginal in the z-space, $N_z(0, z)$, and the associated initial weights are set to $w_0^{(i)} = \int_{\Omega_z} N_z(0, z)dz / N_z(0, z_0^{(i)})$. When sampling from the initial density is not feasible, the samples can be drawn from a uniform distribution instead.
2) For each sample $z_0^{(i)}$, solve the characteristic equation (8) together with the weight dynamics (9)

$$\begin{aligned} \dot{z}^{(i)}(t) &= f_z(z^{(i)}(t)) & z^{(i)}(0) &= z_0^{(i)} \\ \dot{w}^{(i)}(t) &= \operatorname{div}_z(f_z(z^{(i)}(t)))w^{(i)}(t) & w^{(i)}(0) &= w_0^{(i)} \end{aligned} \tag{12}$$

obtaining a family of characteristic trajectories with weights $\mathcal{Z} = \{(z^{(i)}(t), w^{(i)}(t)) \mid i = 1, \ldots, K\}$.
3) For each characteristic trajectory $(z^{(i)}(t), w^{(i)}(t)) \in \mathcal{Z}$, solve the growth-related PBE (11), yielding the solution $\tilde{N}^{(i)}(t, y)$.

The result of our simulation scheme is a family of density functions $\tilde{N}(t, y)$ evolving on the characteristic trajectories $z(t)$ with weights $w(t)$.

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TABLE 1. Formulas for output quantities from the hybrid simulation scheme.

Output quantity	Exact formula	Approximation from simulation
Moments of intracellular variables	$\mu_\alpha(t) = \int_\Omega x^\alpha N(t,x)dx$	$\frac{1}{K}\sum_{i=1}^{K}\int_{\Omega_y}\binom{y}{z^{(i)}(t)}^\alpha \tilde{N}^{(i)}(t,y)dy$
Marginal for the y variables	$N_y(t,y) = \int_{\Omega_z} N(t,y,z)dz$	$\frac{1}{K}\sum_{i=1}^{K}\tilde{N}^{(i)}(t,y)$
Marginal for the z variables	$N_z(t,z) = \int_{\Omega_y} N(t,y,z)dy$	$N_z(t,z^{(i)}(t)) \approx \frac{1}{w^{(i)}(t)}\int_{\Omega_y}\tilde{N}^{(i)}(t,y)dy$

For high-dimensional models, it is usually not practical to interpret the full cell number density $N(t,x)$. Instead, one often evaluates either marginal densities, i.e., the integral of $N(t,x)$ over a subspace that is not of interest, or moments, for example, average concentration values within the population. With the here proposed simulation scheme, the integrals can be approximated by MC integration, with formulas for the relevant output quantities given in Table 1.

Frequently, moments for subpopulations are also of practical relevance, where a subpopulation is defined by all cells having an intracellular variable z within a certain set $\mathcal{S} \subset \Omega_z$. Such moments are approximated from the simulation results by summing only over samples that are within the considered subpopulation, according to the formula

$$\mu_{\alpha,\mathcal{S}}(t) \approx \frac{1}{\#\mathcal{I}(t)}\sum_{i\in\mathcal{I}(t)}\int_{\Omega_y}\binom{y}{z^{(i)}(t)}^\alpha \tilde{N}^{(i)}(t,y)dy \qquad (13)$$

where the sum is over the index set $\mathcal{I}(t) = \{i | z^i(t) \in \mathcal{S}\}$.

B. SIMULATION CASE STUDY

We illustrate the proposed simulation method on a population model for a differentiating cell population. The intracellular dynamics are given by the osteochondroswitch model [9], which describes the differentiation of mesenchymal progenitor cells into either bone cells (osteoblasts) or cartilage cells (chondrocytes). The core model contains three state variables, each corresponding to the gene activity that is characteristic for one of the considered cell types. They which are denoted by z_P, z_O, and z_C, corresponding to gene activity of progenitor, osteoblast, and chondrocyte cells, respectively. We extend that model toward a heterogeneous population model by introducing the cell volume y and a differentiation sensitivity, similarly as in the agent-based model version considered in [4]. The resulting intracellular model thus has five state variables.

Note that even though the method has been formulated for deterministic intracellular dynamics, it is straightforward to apply the approach to models where the nongrowth variables evolve stochastically. For that, the characteristic equation (8) becomes a stochastic differential equation (SDE), which is solved numerically with suitable solvers. For the osteochondroswitch, we model the logarithm of the differentiation sensitivity stochastically with an Ornstein–Uhlenbeck process, which is given by the SDE

$$dz_d = -\theta z_d dt + \sigma dW \qquad (14)$$

with $\theta = 1.93 \cdot 10^{-3}$ min^{-1}, $\sigma = \sqrt{\theta}$, and initial condition sampled from the resulting stationary distribution. The time constant θ is chosen to give an autocorrelation time of 6 h, and the coefficient of variation is adjusted to about 15%, which corresponds well to experimental observations in heterogeneous cell populations. The SDE (14) yields the differentiation sensitivity $\widetilde{m}_P(t) = m_P \cdot 10^{0.05 z_d(t)}$, with the nominal value $m_P = 8.0$. The stochastic differentiation sensitivity feeds into the differential equation for the gene activities, given by

$$\begin{aligned}
\dot{z}_P &= \frac{a_P z_P^n + b_P}{\widetilde{m}_P(t) + u_D(t) + c_{PP} z_P^n} - k_P z_P \\
\dot{z}_O &= \frac{a_O z_O^n + b_O + u_O(t)}{m_O + c_{OO} z_O^n + c_{OC} z_C^n + c_{OP} z_P^n} - k_O z_O \\
\dot{z}_C &= \frac{a_C z_C^n + b_C}{m_C + c_{CC} z_C^n + c_{CO} z_O^n + c_{CP} z_P^n} - k_C z_C .
\end{aligned} \qquad (15)$$

All parameters and initial conditions for (15) were set to their values from [9].[1] A family $\mathcal{Z}$ of 300 characteristic trajectories was generated by solving (14) and (15), 30 of which are shown in Fig. 1. Thereby, a time-varying osteogenic differentiation stimulus $u_D(t)$, $u_O(t)$ has been applied as indicated in Fig. 1.

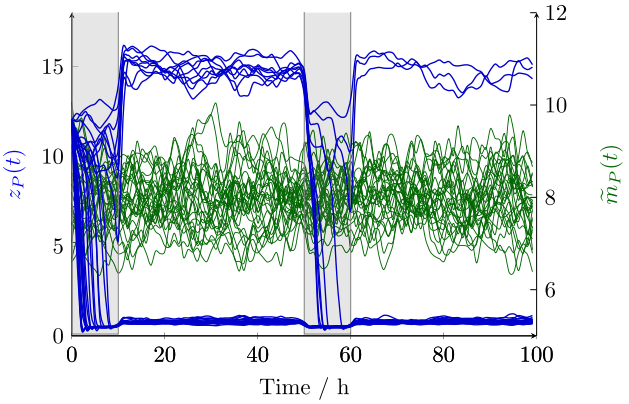

FIGURE 1. Time courses for 30 characteristic trajectories of the intracellular dynamics in the osteochondroswitch model (16) and (17). Gray rectangles show time intervals during which an osteogenic differentiation stimulus was active ($u_D = 3.0$ and $u_O = 0.5$).

The model's only growth variable is the cell volume y. Cell growth is modeled with a ramp function depending on the

[1]See also the original model's reference SBML implementation at http://www.ebi.ac.uk/biomodels-main/BIOMD0000000493.

activity of the progenitor variable z_P:

$$\dot{y} = f_y(z_P) = \begin{cases} 0, & z_P < 5 \\ g_{\max}(z_P - 5)/5, & 5 \le z_P < 10 \\ g_{\max}, & z_P \ge 10 \end{cases} \quad (16)$$

with maximal growth rate $g_{\max} = 5.56 \cdot 10^{-3}\ \mathrm{h}^{-1}$. In that model, only progenitor cells do grow, while differentiated osteoblasts are resting and do not increase in size.

The cell division is modeled in the PBE (11) with a breakage rate function given by

$$b(y) = 0.1\ \mathrm{h}^{-1} y^3. \quad (17)$$

For simplicity, we assume equal partitioning as breakage kernel, $\varphi(y, \eta) = \delta(2y - \eta)$, and no cell death $d(y, z) = 0$.

From solving the PBE (11) along all characteristic trajectories, the growth dynamics for each cell type are obtained. The initial number density distribution in y is taken to be normal with mean 3 and standard deviation 0.03. Fig. 2 shows the total population volume (first moment $\mu_1(t)$ of the number density function in cell volume y) for the progenitor cell and differentiated cell populations separately. These results show that the model captures partial differentiation of the population during differentiation stimulus pulses and regrowth of the progenitor cell population during times where no stimulus is applied, similar to the results in [4].

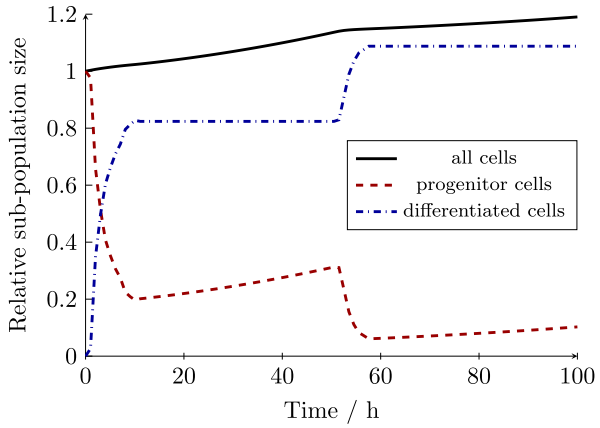

FIGURE 2. Population growth curves for individual subpopulations defined by the intracellular state. A cell is a progenitor cell if $z_P \ge 5$, and a differentiated cell otherwise.

MC simulation algorithms always face a tradeoff between computational cost and approximation error [1]. In order to evaluate the computational efficiency of the proposed hybrid method, we compared its numerical properties with the individual-based method from [4]. We performed ten simulation replicates, parameterized such that the same post-processing time is required for both methods to generate cell number estimates from the single-cell trajectories. From the ten replicates, we computed the average relative width of the resulting 95% confidence interval (CI). The CI width is shown in Table 2 together with the average total length of single-cell trajectories utilized per replicate and the average postprocessing time. These results indicate that the hybrid method achieves a smaller simulation replication error with fewer trajectories and about the same postprocessing time compared with the individual-based method.

TABLE 2. Comparison of numerical characteristics between individual-based [4] and hybrid (this letter) simulation method.

	Individual-based	Hybrid
Total length of trajectories	$1.4 \cdot 10^5$ h	$2 \cdot 10^3$ h
Post-processing time	23.6 min	21.1 min
Relative CI width	12.3%	4.0%

IV. DISCUSSION

In conclusion, the simulation method introduced here permits the efficient computational solution of cell population balance models with high-dimensional intracellular dynamics. We compute a sample-based approximation by generating sample trajectories for the nondivision relevant part. Yet, unlike established MC methods [6], we still simulate a low-dimensional continuous PBE on the sample trajectories. This type of hybrid approach allows us to generate smooth model solutions even with a relatively small number of sample trajectories for the cellular variables.

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